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EXAMINER	
GABEL, GAILENE	
ART UNIT	**PAPER NUMBER**
1641	8

DATE MAILED: 09/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,802	NAKAMURA, REIKO M.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE f this communicati n appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 4/15/03 in Paper No. 7 is acknowledged and has been entered. Claims 21, 23, and 28 have been amended. Claim 30 has been added. Accordingly, claims 21-30 are pending and are under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 112

2. In light of Applicant's amendment and arguments, the rejection of claims 21-29 under 35 U.S.C. 112, second paragraph, is hereby withdrawn.

Rejections Maintained

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

3. Claims 21-23, 25-27, and 29 stand rejected under 35 U.S.C. 102(a) as being clearly anticipated by Katsuhide et al. (JP 09206092, electronic translation version) for reasons of record.

Katsuhide et al. disclose a transdermal delivery device comprising an antigen composition including a phosphate buffered solution for promoting transdermal delivery of the antigen, and a holding portion, i.e. plaster, which contains the antigen composition for use in delayed-hypersensitivity reaction measurement of immunity against infectious disease such as tuberculosis by a tubercle bacillus. The antigen is isolated from Mycobacterium bovis (BCG bacillus) culture. The mycobacterial antigens include MPB64, MPB59, MPB70, and MPB80. The antigen composition is formed into ointment, glycerol, or polyethylene glycol then infiltrated into a strap or plaster for contact and application into skin of human or animal; i.e. patch test to effect transdermal delivery of the antigen (see claims 5-8 and pages 4-5). After topical application of the ointment into skin by a patch, an allergic reaction in the form of a hardening phenomenon on the skin area is caused by the existence of antibody to said mycobacterial antigens (see page 3, lines 3-10).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claim 24 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Katsuhide et al. (JP 09206092, electronic translation version).in view of (1) Haga et al.

(Tubercle and Lung Disease, June 1994, Supp. No. (196)) or (2) Haga et al. (Jpn. J. Med. Sci. Biol, 1996) for reasons of record.

Katsuhide et al. has been discussed supra. Katsushide et al. fail to teach that the antigen is derived from *Mycobacterium tuberculosis, Mycobacterium avium-intracellulare, Mycobacterium kansasii, Mycobacterium fortuitum, Mycobacterium chelonae, Mycobacterium leprae, Mycobacterium africanum, and Mycobacterium microti*, as recited in claim 3.

(1) Haga et al. teach a mycobacterial protein, MPB64 which is isolated from Mycobacterium bovis. (1) Haga et al. further teach that MPB64 gene was detected in other mycobacterial species via polymerase chain reaction such as *M. tuberculosis, M. africanum, and M. microti.* Another mycobacterial antigen, MPB70 protein, likewise, has the same distribution pattern as MPB64.

(2) Haga et al. disclose mycobacterial antigen MPB64, a secretory protein isolated from M. bovis culture filtrate which corresponds to the secretory protein isolated from M. tuberculosis denoted as MPT64. Both MPB64 and MPT64 have identical protein structure on the basis of gene analysis and is therefore designated as MPB/T64, hereinafter, referred to as MPB64. MPB64 is highly specific to M. tuberculosis complex and is, therefore, an ideal antigen for diagnosis of tuberculosis (see Introduction). In their studies, (2) Haga et al. showed that detection of MPB64 by delayed skin reaction correlated well with development of tuberculosis in guinea pigs (see page 25 and Figures 6 and 7).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to isolate, derive, and identify MPB64 from other mycobacterial species such as *M. tuberculosis, M. africanum and M. microti* such as taught by (1) Haga for incorporation into the transdermal delivery device taught by Katsushide, because (1) Haga specifically isolated MPB64 from *M. tuberculosis, M. africanum and M. microti* using PCR. Further, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of (2) Haga into the teaching of Katsuhide because (2) Haga specifically taught that MPT64 of *M. tuberculosis* and MPB64 of M. bovis (also taught by Katsuhide) have identical protein structures and have a high specificity to *M. tuberculosis* complex. Given the teaching that delayed skin reaction observed in guinea pigs correlates well with the development of tuberculosis, one of ordinary skill in the art would have been motivated to incorporate the teaching of (2) Haga or (2) Haga into the transdermal delivery device of Katsuhide because it allows for accurate diagnosis of tuberculosis infection in humans without the need for invasive procedures.

5. Claims 28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katsuhide et al. (JP 09206092, electronic translation version) in view of Barchfield et al. (US 5,709,879) for reasons of record.

Katsuhide has been discussed supra. Katsuhide et al. fail to specifically teach polyoxyethylene sorbitan derivative as a surfactant for use in the instant invention.

Barchfield et al. disclose a combination of adjuvant components, i.e. liposome/antigen component and emulsion component which act together to produce elevated immune response which is useful in delivering antigens to cells and inducing immunity against said antigen (pathogen) or measuring specific reactivity of antibodies against said antigen. Barchfield et al. disclose that a composition of antistimulatory agent comprising antigen, i.e. killed M. tuberculosis, mixed with mineral oil and emulsifying agent is currently known as complete Freund's adjuvant but is known to cause severe side effects. Barchfield et al. then teach using preferred surfactants designed for and commonly used in biological situations which include polyoxyethylene sorbitan fatty acid ethers sold under the trade name TWEEN, and sorbitan fatty acid ethers sold under the trade name SPAN. These surfactants are sorbitan-based and non-ionic prepared by dehydration of sorbitol, reaction with fatty acid, then reaction with ethylene oxide, i.e. sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan sesguioleate, and sorbitan trioleate which are commercially available under the trademark name TWEEN. TWEEN 80 or polysorbate 80 or polyoxyethylene sorbitan monooleate, is most useful in preparing oil-in-water emulsions and dispersions and solubilizing oils and making anhydrous ointments water-soluble or washable. Antigen masses are selected based on desired dose and volume of the final composition and are adjusted depending on the immunogenic response. The ability of antibodies to distinguish a specific antigenic structure has resulted in their wide use in diagnosis (see columns 15 and 16 and Example 8).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the surfactant in the teaching of Barchfield into the physiologically effective solution in the transdermal device as taught by Katsuhide because Barchfield specifically taught that TWEEN surfactants are commercially known and conventional emulsifying agents applicable in adjuvant combinations such as those infiltrated into the transdermal delivery device taught by Katsushide.

Response to Arguments

6. Applicant's arguments filed 4/15/03 have been fully considered but they are not persuasive.

A) It is noted that no arguments were provided by Applicant to rebut the rejection of claims 21-23, 25-27, and 29 under 35 U.S.C. 102(a) as being clearly anticipated by Katsuhide et al. (JP 09206092, electronic translation version). Thus, lack of rebuttal to the aforementioned rejection is construed to be Applicant's acquiescing to the lack of novelty of the rejected claims as anticipated by Katsuhide et al.

B) Applicant contends that the novel feature of the claimed invention is the ability of the transdermal device is to detect active disease. Applicant specifically argues that the references neither individually nor collectively teach the ability to distinguish between active mycobacterial infection versus prior immunologic exposure, i.e. immune or vaccinated patients. Applicant argues that the transdermal device in the instant invention is able to distinguish between these two populations. Applicant argues that

one skilled in the art would not have recognized this important aspect of the present invention using the combination of Katsushide in view of Haga.

In response, the elements required by the claimed invention, specifically claims 21-23, 25-27, and 29, i.e. an antigen composition comprising an antigen, i.e. MPB64, and a physiologically effective solution for use in transdermal delivery; and an antigen holding portion, i.e. plaster or patch, are all taught by Katsushide et al. Alternatively, no distinct requirement is recited in the claims to obviate the teaching of Katsushide or to render the claims as patentably distinct. Further, no distinct requirement is recited in the claims to obviate the suggested combination of Katsushide with (1) Haga or (2) Haga since both taught that MPB64 can be derived from other Mycobacteria including M. tuberculosis. As such, it is inherent that the transdermal delivery device as taught by Katsushide et al. and as combined with (1) Haga or (2) Haga, having all the requirements of the claimed invention, should inherently be able to effect an immunogenic response on skin as indicative of an active disease such as recited in the claimed invention. No specific patentable distinction is seen.

C) Applicant argues that one skilled in the art would not have combined Barchfield with the composition and method of Katsushide because the emulsion taught by Barchfield is administered systemically and not administered transdermally.

In response, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the

references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In this case, Katsuhide et al. disclose a transdermal delivery device having an antigen, a phosphate buffered solution for promoting transdermal delivery of the antigen, and plaster for use in delayed-hypersensitivity reaction measurement of immunity against infectious disease such as tuberculosis. The antigen includes mycobacterial MPB64. The antigen composition is infiltrated into a strap or plaster for contact and application into skin of human or animal to effect transdermal delivery of the antigen then an allergic reaction in the form of a hardening phenomenon on the skin area is caused by the existence of antibody to said mycobacterial antigens. Barchfield was incorporated thereto for the teaching of adjuvant components in combination with preferred surfactants which include polyoxyethylene sorbitan fatty acid ethers to prepare oil-in-water emulsions and ointments for use with desired antigen compositions. Accordingly, the rejection is based on the obvious incorporation of the surfactant in the teaching of Barchfield into the physiologically effective solution in the transdermal device as taught by Katsuhide because Barchfield specifically taught that TWEEN surfactants are commercially known and conventional emulsifying agents applicable in antigen compositions such as those infiltrated into the transdermal delivery device taught by Katsushide.

6. No claims are allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday, Tuesday, and Thursday, 5:30 AM to 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-0169.

Gailene R. Gabel
August 28, 2003

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641